Id3 upregulates BrdU incorporation associated with a DNA damage response, not replication, in human pancreatic beta-cells.

Journal: Islets

Publication Year: 2011

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PubMed link: 21964314

Funding Grants: Interdisciplinary Stem Cell Training Program at UCSD II

Public Summary:
Elucidating mechanisms of cell cycle control in normally quiescent human pancreatic β-cells has the potential to impact regeneration strategies for diabetes. Previously we demonstrated that Id3, a repressor of basic Helix-Loop-Helix (bHLH) proteins, was sufficient to induce cell cycle entry in pancreatic duct cells, which are closely related to β-cells developmentally. We hypothesized that Id3 might similarly induce cell cycle entry in primary human β-cells. To test this directly, adult human β-cells were transduced with adenovirus expressing Id3. Consistent with a replicative response, β-cells exhibited BrdU incorporation. Further, Id3 potently repressed expression of the cyclin dependent kinase inhibitor p57 (Kip2) , a gene which is also silenced in a rare β-cell hyperproliferative disorder in infants. Surprisingly however, BrdU positive β-cells did not express the proliferation markers Ki67 and pHH3. Instead, BrdU uptake reflected a DNA damage response, as manifested by hydroxyurea incorporation, γH2AX expression, and 53BP1 subcellular relocalization. The uncoupling of BrdU uptake from replication raises a cautionary note about interpreting studies relying solely upon BrdU incorporation as evidence of β-cell proliferation. The data also establish that loss of p57 (Kip2) is not sufficient to induce cell cycle entry in adult β-cells. Moreover, the differential responses to Id3 between duct and β-cells reveal that β-cells possess intrinsic resistance to cell cycle entry not common to all quiescent epithelial cells in the adult human pancreas. The data provide a much needed comparative model for investigating the molecular basis for this resistance in order to develop a strategy for improving replication competence in β-cells.

Scientific Abstract:
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